

## REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Claims 1-23 are presently pending, and claims 6 and 18-23 are currently under consideration. By this amendment, claims 19 and 22 are cancelled, and claims 6 and 18 are amended to more clearly recite specific aspects of the invention. Support for the amendments may be found throughout the claims and specification as originally filed, and the amendments do not constitute new matter. The amendments are not to be construed as acquiescence to any rejection and are made without prejudice to prosecution of any subject matter modified by amendment in a related divisional, continuation, or continuation-in-part application.

### Objection to the Specification

The Action objects to the specification as allegedly not providing the serial number for the application filed August 29, 2000 and not clearly defining the relationship between the present application and PCT/US00/18061.

Applicants note that the specification has been amended to recite the serial number for the application filed August 29, 2000 and to define the relationship between the present application and PCT/US00/18061. Accordingly, Applicants respectfully request that this objection be withdrawn.

Applicants note also that the filing date of PCT/US00/18061 was incorrectly recited in the specification and has been amended to correct this error.

### Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 6 and 18-23 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to enable the skilled artisan to make and/or use the invention. More specifically, the Action alleges that the instant specification does not demonstrate that overexpression of a polypeptide encoded by SEQ ID NO:808, or a polypeptide containing a fragment of a polypeptide encoded by SEQ ID NO:808, is associated with cancer. The Action also alleges that the instant specification does not establish that overexpression of a variant of the polypeptide encoded by SEQ ID NO:808 is

associated with cancer. In addition, the Action alleges that the specification does not demonstrate that the polynucleotide of SEQ ID NO:808 is overexpressed in any cancer other than lung cancer. Finally, the Action appears to allege that the claimed methods are not enabled, because the specification does not define a predetermined cut-off value, and, consequently, it is unclear regarding the quantity of polypeptide required to be indicative of cancer.

Applicants respectfully traverse this rejection.

As an initial matter, Applicants submit that the skilled artisan would understand the instant specification to clearly establish that polypeptides encoded by SEQ ID NO:808 are overexpressed in lung tumor tissue as compared to normal lung tissue. Applicants note that SEQ ID NO:808 corresponds to a full length cDNA sequence for the lung tumor antigen designated L552S. Applicants submit that L552S polynucleotide sequences were identified based upon their differential expression in lung tumor tissue as compared to normal lung tissue, as described on page 157, line 7, to page 161, line 3. Furthermore, subsequent mRNA expression analysis confirmed the lung tumor-associated expression of L552S polynucleotides, as described, *e.g.*, on page 159, line 15, to page 161, line 3, and which *per se* indicate overexpression.

Applicants submit that a skilled artisan would further recognize that polypeptides encoded by SEQ ID NO:808 are overexpressed in lung tumor tissue as compared to normal tissue, based upon the disclosure that polynucleotides encoding said polypeptides are overexpressed in lung cancer. One of ordinary skill in the art would understand that polypeptide expression levels are directly linked to mRNA expression levels, since expression of mRNA is absolutely required for protein expression. Furthermore, one of ordinary skill in the art is apprised of the fact that overexpression of an mRNA generally translates to overexpression of its encoded polypeptide. Nonetheless, Applicants have submitted with this amendment a copy of the Declaration of Gary Fanger, Ph.D., which was previously submitted and made of record in copending U.S. Patent Application Serial Number 09/614,124. The Declaration presents data obtained from immunohistochemistry analyses using anti-L552S antibodies and clearly confirms that L552S polypeptides are overexpressed in lung cancer as compared to normal lung tissue. Thus, Applicants submit that the specification, as originally filed, establishes that the overexpression of L552S polypeptides is indicative of lung cancer.

Regarding the Action's position that the instant disclosure does not enable the claimed methods as directed to polypeptides comprising fragments or variants of an L552S polypeptide, Applicants respectfully submit that the skilled artisan would recognize that agents that bind to polypeptides comprising L552S fragments or variants may also be used according to the invention. However, to expedite prosecution and without acquiescence to this basis of rejection, claim 6 has been amended to specify the use of an agent that binds to a polypeptide encoded by SEQ ID NO:808, claim 18 has been amended to specify the use of an agent that binds to a polypeptide having at least 90% identity to a polypeptide encoded by SEQ ID NO:808, and claim 19 has been cancelled. Applicants submit that the skilled artisan would understand from the instant specification and general knowledge in the art that naturally-occurring variants of L552S cDNAs, *e.g.*, allelic variants and polymorphs, may encode L552S polypeptides having one or more amino acid substitutions, deletions, or additions. Accordingly, such variant L552S polypeptides may contain one or more additional or different binding sites, *e.g.*, epitopes, but, nevertheless, would still be able to bind the polypeptide of SEQ ID NO:809. Applicants further submit that the skilled artisan would immediately recognize that such variants would very likely also be overexpressed in lung cancer, since they would be expressed from the same gene and their expression would be regulated by the same regulatory control elements as L552S polynucleotides of SEQ ID NO:808. Accordingly, the skilled artisan would realize that binding agents that recognize such variants could be used according to the invention. In addition, Applicants submit that the instant specification teaches the skilled artisan how to produce agents that bind to L552S polypeptides and fragments or variants thereof. For example, the instant specification teaches how to produce L552S polypeptides and generate polyclonal antibodies specific for L552S polypeptides (*See, e.g.*, page 118, line 14, - page 119, line 7, and page 123, line 2, - page 124, line 11). Provided with the L552S sequences set forth in SEQ ID NOs:808 and 809, the skilled artisan could readily adapt such methods to produce agents that bind L552S variants and fragments, which could then be used according to the claimed methods to detect lung cancer.

Applicants further submit that the skilled artisan could readily determine an appropriate cut-off value, particularly in light of the instant specification, which describes a three-fold or greater increase in the amount of bound polypeptide detected in a test patient

sample as compared to a non-cancerous control sample as typically positive for cancer (page 148, lines 19-21). Provided with this information, the skilled artisan could determine the amount of bound L552S polypeptide detected in one or more normal lung tissue samples and, based on this value, determine an appropriate cut-off value. Applicants submit that such a determination would require merely routine screening and not undue experimentation. In addition, the instant specification provides exemplary cut-off values and methods of determining the same. In one embodiment, cut-off values are described as the average mean signal obtained when an immobilized antibody is incubated with samples from patients without the cancer (page 151, lines 24-27). In an alternate embodiment, the cut-off value is determined using a Receiver Operator Curve, as described on page 151, line 28, - page 152, line 11. Applicants further note that the designation of an absolute cut-off value is scientifically inappropriate, since the methods of the invention may be practiced using a variety of techniques, each of which would likely exhibit different sensitivities and, therefore, produce different control and appropriate cut-off values. Thus, Applicants submit that the disclosure provides adequate guidance regarding the selection of a cut-off value and, thus, provides reasonable enablement for the claimed method. Indeed, the situation is analogous to claims directed to a therapeutically effective amount of a compound, where courts have recognized that determining effective dosage for a pharmaceutical agent against a particular disease is well within the ordinary skill in the art. *In re Bundy*, 209 U.S.P.Q. 48 (C.C.P.A. 1981). Applicants respectfully request that this basis of rejection be withdrawn.

*Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description*

Claims 6 and 18-23 also stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking sufficient written description in the specification to support the genus of polypeptides comprising any 10 or 20 residues of a polypeptide encoded by SEQ ID NO:808 or the genus of variants having at least 75% identity to the polypeptide encoded by SEQ ID NO:808.

Applicants respectfully traverse this rejection and submit that the specification provides adequate written description for polypeptides comprising both fragments and variants of L552S polypeptides encoded by SEQ ID NO:808. Under the Examination Guidelines set

forth by the Patent and Trademark Office, the written description requirement for a claimed genus may be satisfied by the description of a representative number of species or the disclosure of relevant, identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, ¶1, “Written Description” Requirement, 66 Fed. Reg. 1099, at 1106. Applicants submit that the instant application meets both criteria.

First, Applicants submit that the instant specification describes a representative number of claimed species by providing the sequence of polypeptides encoded by SEQ ID NO:808 as well as describing sequences with at least 75% or 90% identity to these polypeptides. Applicants note that the description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species the genus embraces. *Id.* Applicants submit that by providing a reference sequence and the percent identity limitation, the specification adequately describes a representative number of claimed variants, since one skilled in the art would readily identify a claimed sequence and recognize that Applicants were in possession of said sequence at the time the application was filed.

In addition, Applicants submit that the instant specification discloses sufficient identifying characteristics for L552S-related polypeptides that are common to the genus of polypeptides with at least 75% or 90% identity to a polypeptide encoded by SEQ ID NO:808, since it provides both a reference sequence and percent identity limitations. Polypeptides of this genus clearly share the structural characteristic of at least 75% or 90% identity with a polypeptide sequence encoded by SEQ ID NO:808. Moreover, Applicants submit that the instant application satisfies both the possession and notice functions of the written description requirement, since one of skill in the art would clearly be able to recognize and identify an L552S polypeptide variant based upon the instant specification and would also understand that Applicants had possession of said polypeptides at the time the application was filed.

Applicants further submit that the instant specification provides adequate written description to support claims directed to polypeptides comprising fragments of L552S polypeptides encoded by SEQ ID NO:808. Applicants submit that by providing the polynucleotide sequence of SEQ ID NO:808 and its encoded polypeptide sequence (SEQ ID NO:809), the specification clearly provides written description for fragments of the encoded

polypeptide sequence. Applicants submit that the skilled artisan would readily appreciate that Applicants were in possession of fragments of the polypeptides they identified, including polypeptides encoded by SEQ ID NO:808.

Further still, Applicants submit that the tumor-associated expression profile identified by Applicants for polypeptides encoded by SEQ ID NO:808 offers yet another important identifying characteristic from which the skilled individual would conclude that Applicants were in possession of fragments and variants of the polypeptide encoded by SEQ ID NO:808 at the time this application was filed. One skilled in the art would readily understand that diagnostic methods directed to L552S polypeptides rely upon the tumor specificity of polypeptides encoded by SEQ ID NO:808, a property only first identified by Applicants instant disclosure. Furthermore, one skilled in the art would recognize that these uses do not necessarily require a polypeptide with the exact or entire sequence of a full length L552S polypeptide. Polypeptide variants and fragments may be used, for example, to generate antibodies against L552S polypeptides, and such antibodies would be useful in the detection of cancer in the context of Applicants' disclosure. Furthermore, the skilled artisan would expect that such fragments, to the extent they are contained within L552S polypeptides encoded by SEQ ID NO:808, were indeed in the possession of Applicants at the time of filing.

However, to expedite prosecution and without acquiescence to this basis of rejection, claim 6 has been amended to specify the use of an agent that binds to a polypeptide encoded by SEQ ID NO:808, claim 18 has been amended to specify the use of an agent that binds to a polypeptide having at least 90% identity to a polypeptide encoded by SEQ ID NO:808, and claim 19 has been cancelled. In light of these amendments and remarks, Applicants submit that the instant application clearly provides written description of the claimed invention and respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 8 and 18-23 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite in the recitation of "predetermined cut-off value." More specifically, the Action alleges that the instant specification does not provide a clear definition of the phrase

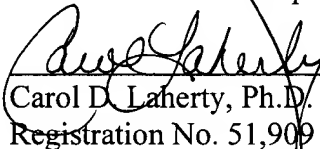
and there is no art recognized definition of the phrase, so the skilled artisan would be unable to determine what is encompassed by the phrase.

Applicants respectfully traverse this basis of rejection. Applicants submit that the skilled artisan would readily understand the meaning of the phrase "predetermined cut-off value," based upon general knowledge in the field and the description in the instant specification. In addition, Applicants submit that the instant specification explicitly describes exemplary cut-off values and methods of determining the same. In one embodiment, cut-off values are described as the average mean signal obtained when an immobilized antibody is incubated with samples from patients without the cancer (page 151, lines 24-27). In an alternate embodiment, the cut-off value is determined using a Receiver Operator Curve, as described on page 151, line 28, - page 152, line 11. Accordingly, Applicants submit that the skilled artisan would understand the metes and bounds of the claimed invention and request that the rejection be withdrawn.

The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. Applicants' attorney wishes to express her willingness to engage in a telephone interview to further the status of this application if any further concerns need to be addressed.

Respectfully submitted,  
Tongtong Wang et al.  
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Enclosure:

Postcard

Copy of Declaration previously submitted in copending U.S. Serial No. 09/614,124

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